REMARKS

By the present communication, claim 1 is amended to correct the misspelling of crospovidone. No new matter is introduced as the amended language is supported by the application as filed. Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and the reasons set forth below.

I. Rejections Under 103 (a)

Claims 1-6 stand rejected under 35 U.S.C. § 103(a), as being allegedly unpatentable over Damien *et al.*, *Clin. Pharmco.* 37 (1999) Suppl 1 (XP009004369) in view of Tobin *et al.*, U.S. Patent No. 6,077,534, and further in view of Conte *et al.*, U.S. Patent No. 6,294,200. In the pending Action (p. 3, lines 7-8), the Office asserts that Damien *et al.* discloses the claimed sustained release tablet composition, but teaches povidone instead of copovidone and does not teach the use of hypromellose with the claimed viscosity range. The Office further contends that in view of the teachings of Tobin *et al.*, it would have been obvious to one skilled in the art to use copovidone in place of povidone in order to improve the binding and sustained release properties of the tablet (*Id.*, lines 8-16; p. 4, lines). Furthermore, the Office reasons that it would be obvious to include hypromellose of the viscosity range of the '200 patent in order to obtain the formulation with better controlled release of the drug compounds (*Id.*, lines 17-22). Because the cited art does not in fact teach such modifications, and because the present formulation provide unexpectedly superior results, Applicant respectfully submits that the claimed invention is nonobvious.

As admitted by the Office, Damien *et al.* fails to teach among other things, the use of copovidone in a sustained release formulation of indapamide. Because both Tobin *et al.* and Conte *et al.* fail to teach the interchangeability of povidone and copovidone in a sustained release formulation of the type in Damien *et al.*, the combination of these three references fails to render the claimed invention obvious. Further, even if the cited references established a prima facie case of obviousness, Applicant submits that the claimed formulation exhibits unexpected results that could not have been predicted. Thus, the claimed invention is nonobvious over the cited art.

First, contrary to the assertion in the Office Action (p. 4, lines 17-10), Tobin *et al.* lacks any teaching that substitution of copovidone for povidone increases the binding of the formulation and prolongs release of a drug. In fact, Tobin *et al.* does not rely on the use of copovidone to provide sustained release of the active ingredient, dried horse chestnut extract (HCE). Rather, Tobin *et al.* discloses a method of producing HCE as pellets (col. 3, lines 49-51) and achieving sustained release by coating the pellets (col. 4, lines 32-34; col. 8, lines 44-45). In such diffusion pellets, "the active ingredient is released across the fine pored water-insoluble permeable coating of the above-said coated pellets." col. 2, lines 55-58. The pellet coating is formed from a mixture of acrylates (col. 5, lines 39-44; col. 8, lines, 44-51). There is simply no teaching that povidone or copovidone, which do not make up the coating, have any effect on the sustained release properties of the composition and therefore no reason that the skilled artisan might expect copovidone to prolong release of the drug or be useful in the formulation of Damien *et al.*

Likewise, Conte *et al.* fails to teach or suggest the interchangeability of povidone and copovidone in a sustained release formulation of the type in Damien *et al.* Indeed, copovidone is not mentioned in Conte *et al.* Hence, Conte *et al.* cannot cure this deficiency of Tobin *et al.*

Further, Conte *et al.* fails to teach or suggest the use of hypromellose having the claimed viscosity range in a formulation of the type in Damien *et al.* In contrast to the formulation in Damien and the claimed formulation, Conte *et al.* discloses a tablet formulation characterized by a three-layer core and a partial coating (Abstract; col. 2, lines 18-39; col. 3, lines 19-51). The partial coating may include hydroxypropylmethylcellulose and is applied "on the whole lateral surface and on the lower base of said three layered core" (claim 1). The partial coating forms "an impermeable barrier which resists dissolution for a predetermined period of time while allowing for the release of the active substance both from the upper layer and from the lower layer." Hence, the partial coating is not mixed with active substance, outlasts the three-layer core which does have the active substance, and is not primarily responsible for the sustained release properties. In view of these facts, Conte *et al.*'s disclosure that hydroxypropylmethylcellulose in

the partial coating may have a viscosity from 4,000 to 100,000 cP in no way teaches or suggests Applicant's much narrower range of 1,000-20,000 cP for hypromellose contained in the tablet.

Moreover, Applicant now presents comparative data regarding the surprising and unexpected effect that the use of copovidone in conjunction with hypromellose has on the formulation. As disclosed in the Declaration of Ms. Katarzyna Jureczek (submitted herewith), the use of copovidone significantly and unexpectedly provides a generally smaller granulate size than povidone. Dec., ¶¶ 2-8. For the reasons set forth below, this is important to the homogeneity of the formulation and the controlled release of indapamide.

To prepare formulations of the invention,

> a wet granulate is formed from indapamide, lactose monohydrate, and a binder. The dried granulate is homogenized with hypromellose and lubricants to provide the sustained release formulation as defined, e.g., by claim 1. Because of the high percentage of hypromellose in the formulation, the size of the granulate affects the homogeneity of the indapamide in the formulation and therefore the control of indapamide release. Hypromellose used in pharmaceutical formulations has a relatively small particle size and will provide the most homogenous formulation when the granulate of active ingredient is of similar size. Surprisingly, it has been found that copovidone, but not povidone, provides a granulate with a superior particle size distribution for use in the present formulation. Dec., ¶ 2.

To illustrate the effect of copovidone on particle size, analyses of the particles sizes of the granulate used to produce the claimed formulation (with copovidone) and the same granulate with povidone were carried out. Dec., ¶¶ 3-6. The two batches of granulates, prepared as disclosed in paragraphs 4-5 of the declaration, were

> fed into a column with sieves of different sizes arranged one below the other from largest (top) to smallest (bottom). Granules too large to pass through the mesh of a particular screen were retained and measured. The amount of residue of granules retained by each

> screen was measured as a percentage of the total mass of the batch separated on the column of sieves." Dec. ¶ 6.

The results of the experiment shows that the granulate containing copovidone exhibits significantly small particle size that the povidone granulate, as detailed in the Table in Exhibit A of the Declaration and explained at paragraph 7:

> [A]t a sieve mesh size of 0.4 mm, 58.45% of povidone comprising granulate is held back (see residues on sieve) and only 16.65% pass. In contrast, at the same sieve mesh size, only 16.75% of the copovidone comprising granulate is held back and as much as 65.60% pass through. Only at the mesh sizes of 0.315 mm is the greatest amount of copovidone comprising granulate held back (35.20%), and nearly as much (28.75%) is held back at the even smaller mesh size of 0.200 mm.

The smaller particles sizes of the copovidone granulate provides for improved homogenization with hypromellose and therefore improved control over the sustained release of the indapamide from the formulation. Dec. ¶ 8. Such an advantage could not be predicted and is not taught or suggested by the cited references.

Accordingly, because the cited references fail to teach or suggest the interchangeability of povidone and copovidone in a sustained release formulation of the type in Damien *et al.*, and because the use of copovidone leads to a surprising and unexpected decrease in granulate size, the claimed invention is nonobvious over the cited references. Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-6 under 35 U.S.C. § 103(a).

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. If any issues remain to be resolved in view of this amendment and reply, the Office is requested to contact the undersigned by telephone to achieve a prompt disposition thereof.

Respectfully submitted,

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